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(54) Title: SURVIVAL BENEFIT

(57) Abstract: The invention relates to a method of treating, and improving survival in, critically ill patients, and the use of certain sterile sedative pharmaceutical compositions for the manufacture of a medicament for improving the survival of such patients; in particular such use of pharmaceutical compositions comprising a free radical scavenging sedative agent (such as propofol) and a metal ion chelating agent (such as edetate) in association with a pharmaceutically-acceptable diluent or carrier, especially such composition comprising an oil-in- water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent (such as disodium edetate).

SURVIVAL BENEFIT

The present invention relates to a method of treating, and improving survival in, critically ill patients, and the use of certain sterile sedative pharmaceutical compositions for the manufacture of a medicament for improving the survival of such patients.

Despite advances in critical care medicine the rate of survival of critically ill patient remains poor, and is quite variable, with typical mortality rates in the range 10% to 40%. Beyond the development of antibiotics and improvements in medical techniques (such as newer resuscitation techniques, for example ventilation and fluids administration) there has probably been little impact on survival rates in critical illness despite many years of medical research involving many drugs and treatment regimes. There is therefore a large unmet medical need for improving the rate of survival in critically ill patients.

Propofol is an intravenous sedative agent and can be used for the induction and maintenance of general anaesthesia and for sedation, for example in Intensive Care Units. Propofol is a highly successful anaesthetic and is marketed under the trademark 'Diprivan' for use in treating humans and under the trademark 'Rapinovet' for veterinary use.

Once the anaesthetic properties of propofol were identified, UK patent application no. 13739/74 was filed and this was granted as UK Patent 1,472,793. Corresponding patents have been granted in the USA (USP 4,056,635, USP 4,452,817 and USP 4,798,846) and many other territories.

The finding that adventitious extrinsic microbial contamination resulting from non-aseptic handling of the original formulation of 'Diprivan' could lead to 'clusters' of post-operative infection, initiated development of a modified formulation with a suitable additive present (the additive being capable of retarding the growth of common micro-organisms to not greater than 1 log increase (ie, 10 fold) in 24 hours following extrinsic contamination equivalent to 'touch contamination'). The development of a modified, edetate-containing formulation of propofol led to the filing and grant, inter alia, of UK Patent No. 2,298,789. Corresponding patents have been granted, for example, in the USA (USP 5,714,520; USP 5,731,355; USP 5,731,356; USP 5,908,869) and in other territories. The marketed modified formulation of 'Diprivan' contains 0.005% disodium edetate.

In order to satisfy FDA Regulations a Clinical Trial Programme was carried out in the US between 1993 and 1998 using the modified formulation of 'Diprivan'. Its objective was to consider what effect the addition of 0.005% disodium edetate to 'Diprivan' has on its

pharmacokinetic, efficacy and safety profile. No differences in pharmacokinetics or efficacy were anticipated. However, it was postulated that it may produce differences in serum calcium and magnesium concentrations, and possibly renal function. These safety parameters were therefore the primary measures in the clinical trial programme.

The programme, involving ten separate clinical trials, confirmed that the addition of disodium edetate (0.005% w/v) did not affect the efficacy or pharmacokinetics of 'Diprivan'. With respect to safety, no clinically significant effects on calcium or magnesium levels were seen and since its introduction, no disturbance of calcium or magnesium homeostasis from either short- or long-term use of the modified formulation has been reported. Indeed, the overall adverse event profile of the modified 'Diprivan' did not appear to be clinically different from that of 'Diprivan'. The only notable effect was a higher excretion of zinc in the urine of intensive care unit (ICU) patients receiving the modified formulation for long-term sedation, compared with those receiving a standard sedative agent. The clinical significance of this finding is unclear, but as a precaution the prescribing information was changed to consider the use of zinc supplementation when administering modified 'Diprivan' as a long-term infusion in patients predisposed to zinc deficiency.

The nature and pattern of spontaneously reported adverse events from all 'Diprivan' use have also been monitored and, although it is not possible to determine precise numbers, the pattern of events reported after introduction of the modified formulation is similar to that prior to its introduction, other than a reduction in 'clusters' of infections associated with adventitious extrinsic microbial contamination. No new or unexpected adverse reactions have appeared, indicating that the addition of disodium edetate has not affected the safety profile of 'Diprivan'. In particular, there has been no increase in the number of reports that might be attributable to toxicity of disodium edetate, e.g. hypocalcaemic symptoms or renal impairment.

The raw data from the clinical trial programme has not been previously made available publicly. Additionally, as stated above, the primary endpoint of these trials was to observe whether there were any (clinically) significant untoward differences in adverse event profile with the modified 'Diprivan' formulation.

We can now report that the data from four of our clinical trials indicates an improvement in survival in certain critically ill patients. Further, a more specific survival/outcomes analysis (not previously required) of the data from these clinical trials has been performed. We report herein for the first time the new results obtained from this

particular, specific analysis. It is often through such fresh analysis of medical data that medical progress is made. Thus, the conclusions and application of the present analysis represent novel and surprising results, not previously disclosed.

In brief, we have now surprisingly found that modified formulation 'Diprivan', i.e. 2,6-diisopropylphenol (propofol) when administered in a formulation containing 0.005% disodium edetate, possesses previously unrecognised properties and is effective in significantly improving survival in certain critically ill patients. The observation of these new properties provides, for example, the opportunity for treating selected patient populations in intensive care units (ICUs) with certain propofol-containing formulations, and in so doing achieving significantly improved survival benefits over alternative sedatives/anaesthetics. The results reported here show, for the first time, that 2,6-diisopropylphenol (propofol) in modified formulation 'Diprivan' has a genuine benefit in improving critically ill patient survival rates, and delivers a new therapeutic strategy for treatment of such patients.

Thus, pharmaceutical compositions containing a free radical scavenging sedative agent (such as propofol) and a metal ion chelating agent (such as edetate) may be of value as a therapy for the improving survival in certain critically ill patients.

Studies comparing the use of propofol with other sedatives (e.g. Midazolam) in ICUs have focused on objectives such as cost, weaning from ventilation and nutrition. Such studies have failed to reveal any benefit in survival or mortality associated with use of any particular sedative. One report analysing 18 trials comparing Midazolam with propofol (without EDTA) in ICU sedation showed similar mortality for propofol and Midazolam (Intensive Care Medicine, 1999, 25 1999 - Suppl 1 pp S158 Abs. - 12th Annual Congress of European Society of Intensive Care Medicine, Berlin, 3-6 Oct. 1999). No study has previously shown a survival benefit for modified 'Diprivan' over other sedative agents.

Given the particular complexity of processes involved in death and multiple organ dysfunction/failure, the effectiveness of modified 'Diprivan' in counteracting the complex events involved in death is genuinely surprising.

Accordingly, the present invention provides a method of improving survival in critically ill patients which comprises administration of a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier.

The present invention further provides a method of improving survival in critically ill patients which comprises administration of a pharmaceutical composition comprising a free-

radical scavenging sedative agent and a metal ion chelating agent, which pharmaceutical composition is described and claimed in United Kingdom Patent 2,298,789.

In particular, the invention provides a method of improving survival in critically ill patients which comprises administration of a sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent.

Yet more particularly, the invention provides a method of improving survival in critically ill patients which comprises administration of a sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises edetate.

The invention further provides a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier, for use as a medicament for improving survival in critically ill patients.

The invention further provides a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, which pharmaceutical composition is described and claimed in United Kingdom Patent 2,298,789, for use as a medicament for improving survival in critically ill patients.

In particular, the invention provides a sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent, for use as a medicament for improving survival in critically ill patients.

Yet more particularly, the invention provides a sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises edetate, for use as a medicament for improving survival in critically ill patients.

The invention further provides the use of a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier, for the manufacture of a medicament for

improving survival in critically ill patients.

The invention further provides the use of a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, which pharmaceutical composition is described and claimed in United Kingdom Patent 2,298,789, for the manufacture of a medicament for improving survival in critically ill patients.

In particular, the invention provides the use of a sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent, for the manufacture of a medicament for improving survival in critically ill patients.

Yet more particularly, the invention provides the use of a sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises edetate, for the manufacture of a medicament for improving survival in critically ill patients.

Further provided are a method and use substantially as described herein with reference to the Experiments and Results.

The methods and uses of the present invention relate to use in warm-blooded animals, such as man, in sedation.

By 'improvement in survival' and 'improving survival' we mean that the critically ill patient is still alive at a clinically significant time, such as 7 days post sedation. A further clinically significant time is 28 days post-sedation. The post-sedation time may be determined from the point at which sedation was commenced (as in the clinical trial programme) or from the point at which sedation was stopped. Also included in these terms is that the critically ill patient demonstrates a reduction, or absence, in condition related problems and/or does not require further mechanical ventilation and/or is deemed by a physician to be less likely to die and/or is deemed by a physician to have an improved probability of surviving.

The patient populations which benefit the most from the invention are 'critically ill patients' and are those not receiving sedation for a chronic disease, i.e. 'critically ill patients' are those, for example, suffering an acute insult, injury or trauma and requiring sedation following, for example, (elective or emergency) surgery, medical treatment or post-trauma. In particular, critically ill ventilated patients in ICUs are included. Patients with a probability of dying (e.g. from an underlying disease condition such as severe renal failure) of about 70% or

above are less likely to benefit from the invention. Similarly, the benefit from the invention will also be less marked for patients who are intrinsically reasonably healthy, with a probability of dying of about 5% or less. The invention thus provides, in one embodiment, a potential treatment for certain patients in danger of suffering multiple organ dysfunction/failure. In another embodiment the use and method of the invention are provided for surgical patients requiring sedation following elective and/or emergency surgery. In a further embodiment the use and method of the invention are provided for critically ill patients with an APACHE II score of below 24, preferably below 19. Preferably the use and method of the invention are provided for patients early in the course of their critical illness (i.e. when the systemic inflammatory response is not fully activated).

We believe the effects described herein result from the combined use of a free-radical scavenging sedative agent and a metal ion chelating agent. These respective components may be administered simultaneously (as in the case of 'Diprivan' with the results reported herein, i.e. combined in one formulation), separately (for example via separate infusion lines) or sequentially (provided that sedation is maintained and an adequate metal-ion chelating agent dose and concentration is maintained in-vivo at the same time). An adequate level of a metal-ion chelating agent is a function of a number of factors, including the patient, their overall & metal ion homeostasis condition and whether the patient is receiving any additional metal ion supplementation. In one embodiment, the metal ion chelating properties and concentrations are those as obtained from disodium edetate in the modified formulation of 'Diprivan' used in the accompanying Experimental & Results.

The components may be administered continuously by infusion (together as a co-infusion or separately) or via intermittent bolus injections. For example, propofol formulations without a metal ion chelating agent may be administered with an independent administration of a metal ion chelating agent.

Without wishing to be constrained by theory, we believe that the effects described herein may arise from a beneficial synergy resulting from a reduction in physiological stress caused by use of the free radical scavenging sedative agent, and a beneficial effect on acute stress responses resulting from use of the metal ion chelating agent. The beneficial synergy is believed to result in lower levels of stress-related agents and/or an anti-oxidative effect.

The benefit reported herein is believed to arise, in part, from the free radical scavenging/anti-oxidative effects of the sedative propofol. Thus, formulations containing other free radical scavenging/anti-oxidative sedatives may also show benefit. By a 'free

radical scavenging sedative agent' we mean a sedative agent that also has the ability to scavenge free radicals in-vivo (with the ability to counteract free radical mediated oxidative stress processes). Apart from propofol, other such agents may include, for example, barbiturates such as phenobarbitol. The free radical scavenging sedative agent is preferably lipophilic in nature.

Benefit is also believed to arise, in part, from the metal ion chelator chelating (trace) metal ions involved in oxidative processes, for example, divalent metal ions involved in enzyme free radical mechanisms leading to apoptosis and cell death. Such metal ions include calcium, iron, zinc and copper. The metal ion chelating agent is preferably hydrophilic in nature. Benefit may be observed by suitable inhibition of calcium influx induced apoptosis (Ca channel blockers, such as Nifedapine, may also be useful in this context) and/or enhanced hypo-zincaemia and/or a reduction in iron serum levels. The particular combination of a (lipophilic) free radical scavenging/anti-oxidative sedative and a (hydrophilic) metal ion chelating agent is believed to be important in achieving a balanced counter to oxidative stress. The lipid component of an oil-in-water emulsion used as a pharmaceutically-acceptable carrier may also provide part of a beneficial synergy. The relative concentrations of components may vary, provided that sedation and adequate metal-ion chelating agent dose and concentration are maintained. The addition of other antioxidants (such as VitaminE) may also exert an additional beneficial effect.

For particular benefit attention should be paid to the following factors :-

1. The time to sedation should preferably be as soon as possible after injury for the most benefit to be observed (typically within 1 to 2 hours), but the time may vary depending on the nature of the particular patient and injury.

2. The duration of treatment should be as long as is considered necessary by an attending physician. The duration of treatment for a benefit to be observed may be longer than that normally required or used in routine practice for mechanical ventilation. Thus, provided a therapeutic effect is expected or is being observed then treatment may be continued. A beneficial effect may be evidenced by, for example, an improvement in, or maintenance of (if a deterioration is usually expected), organ function and/or standard physiological measures such as blood pressure, body temperature and/or a normalisation of immune function. Treatment would usually be for 24 hours or greater.

3. The depth of sedation may be light, moderate or deep depending on the particular patient and the extent of their illness. Sub-sedative doses may also be usefully administered in

certain patients.

4. The dose of components should be sufficient to achieve the desired level of sedation and achieve an adequate metal-ion chelating agent dose. Based on 'Diprivan' dosage levels in the range 0.3-8.0 mg/Kg/hr, doses of disodium edetate in the range $5x10^{-5}$ g/hr to about 0.05 g/hr are appropriate for particular benefit. Equivalent doses of other metal ion chelating agents may be calculated based on these figures.

By 'a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent' we include compositions containing both agents (so permitting simultaneous dosing of each component), and also systems in which each individual component may be dosed separately or sequentially. A further feature of the invention is therefore, a pharmaceutical composition comprising a free-radical scavenging sedative agent, such as a barbiturate, and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier. A preferred pharmaceutically-acceptable diluent or carrier is an oil-in-water emulsion using a water-immiscible solvent (see elsewhere herein for further details).

In pharmaceutical compositions in which the free radical scavenging sedative (such as propofol) and the metal chelating agent (such as edetate) are present in a composition suitable for administration, other additives may also be present (see later under "Combination with other therapeutic agents"). Suitable pharmaceutical compositions containing propofol for use in the present invention are described and claimed in United Kingdom Patent 2,298,789 and US Patent 5,714,520 (the contents of which are hereby incorporated by reference), and corresponding applications/patents in other territories.

By an 'oil-in-water emulsion' we mean a distinct two-phase system that is in equilibrium and in effect, as a whole, is kinetically stable and thermodynamically unstable.

By the term 'edetate' we include metal ion chelating/sequestering agents, such as polyaminocarboxylate chelators, such as 'edetate' (ethylenediaminetetraacetic acid -EDTA), diethylenetriaminepentaacetic acid (DTPA) and EGTA, and derivatives thereof. For example, the disodium derivative of edetate is known as disodium edetate. In general, suitable metal ion chelating agents are those salts having lower affinity for the free acid form than calcium, and in particular those derivatives descibed in UK Patent No. 2,298,789. A particular, preferred metal ion chelating agent is disodium edetate. Desferroxime is a further suitable metal ion chelating agent.

In propofol compositions containing edetate, typically the metal ion chelating agent

will be present in the compositions in a molar concentration (with respect to the metal ion chelating agent free acid) in the range $3x10^{-5}$ to $9x10^{-4}$. Preferably the metal ion chelating agent free acid is present in the range $3x10^{-5}$ to $7.5x10^{-4}$, for example in the range $5x10^{-5}$ to $5x10^{-4}$ and more preferably in the range $1.5x10^{-4}$ to $3.0x10^{-4}$, most preferably about $1.5x10^{-4}$. In particular, the metal ion chelating agent free acid is present in the range from about 0.0005% to 0.1% w/v. The 0.005 % concentration of disodium edetate used in modified 'Diprivan' was selected to prevent significant growth of microorganisms for at least 24 hours in the event of adventitious, extrinsic contamination (see UK Patent No. 2,298,789 - the relevant information from which is hereby incorporated by reference). Depending upon the properties of the metal ion chelating agent selected, the benefit of the present invention may be achieved using lower than a 0.005 % concentration.

A propofol composition suitable for use according to the present invention typically comprises from 0.1 to 5%, by weight, of propofol. Preferably the composition comprises from 1 to 2% by weight of propofol and, in particular, about 1% or about 2%. Propofol alone may be emulsified with water by means of a surfactant, but it is preferred that propofol is dissolved in a water-immiscible solvent prior to emulsification. The water-immiscible solvent is suitably present in an amount that is up to 30% by weight of the composition, more suitably 5-25%, preferably 10-20% and in particular about 10%.

A wide range of water-immiscible solvents can be used in the compositions suitable for use in the present invention. Typically the water-immiscible solvent is a vegetable oil, for example soy bean, safflower, cottonseed, corn, sunflower, arachis, castor or olive oil. Preferably the vegetable oil is soy bean oil. Alternatively, the water-immiscible solvent is an ester of a medium or long-chain fatty acid for example a mono-, di-, or triglyceride; or is a chemically modified or manufactured material such as ethyl oleate, isopropyl myristate, isopropyl palmitate, a glycerol ester or polyoxyl hydrogenated castor oil. In a further alternative the water-immiscible solvent may be a marine oil, for example cod liver or another fish-derived oil. Suitable solvents also include fractionated oils for example fractionated coconut oil or modified soy bean oil. Furthermore, the compositions suitable for use in the present invention may comprise a mixture of two or more of the above water-immiscible solvents.

Propofol, either alone or dissolved in a water-immiscible solvent, is emulsified by means of a surfactant. Suitable surfactants include synthetic non-ionic surfactants, for example ethoxylated ethers and esters and polypropylene-polyethylene block co-polymers,

and phosphatides for example naturally occuring phosphatides such as egg and soya phosphatides and modified or artificially manipulated phosphatides (for example prepared by physical fractionation and/or chromatography), or mixtures thereof. Preferred surfactants are egg and soya phosphatides.

The compositions suitable for use in the present invention are suitably formulated to be at physiologically neutral pH, typically in the range 6.0-8.5, if necessary by means of alkali such as sodium hydroxide.

The compositions suitable for use in the present invention may be made isotonic with blood by the incorporation of a suitable tonicity modifier for example glycerol.

The compositions suitable for use in the present invention are typically sterile formulations and are prepared according to conventional manufacturing techniques using for example aseptic manufacture or terminal sterilisation by autoclaving. Further details on the preparation of compositions suitable for use in the present invention are included in the Patents referred to herein in the introduction, and are hereby incorporated by reference.

The compositions suitable for use in the present invention are useful as anaesthetics, which includes sedation and induction and maintenance of general anaesthesia, and such properties may be usefully exploited during the improvement in survival in critically ill patients according to the present invention. Propofol is a short-acting anaesthetic, suitable for both induction and maintenance of general anaesthesia, for sedation to supplement regional analgesic techniques, for sedation of ventilated patients receiving intensive care and for conscious sedation for surgical and diagnostic procedures in Intensive Care Units. Propofol may be administered by single or repeated intravenous bolus injections or by continuous infusion. It is very rapidly removed from the blood stream and metabolised. Thus the depth of sedation is easily controlled and patient recovery on discontinuing the drug is usually rapid and the patient is often significantly more clear headed as compared to after administration of other anaesthetics.

The dosage levels suitable for improving survival in critically ill patients according to the invention are generally within those typically used for sedation. For 'Diprivan', dose levels in the range 0.3-8.0 mg/Kg/hr for adult humans may be used, but may be optimised to achieve the desired effect in any particular patient, in accordance with normal skill in the art. A continuous infusion at about 0.3-4.0 mg/kg/hr for sub- to moderate sedation is typically used. See US 5,714,520 for further information on dosing, the contents of which are hereby incorporated by reference.

In use, the propofol composition of the present invention may be administered for longer than is used for simple sedation, i.e. a patient may thus be maintained under sedation until it is considered that effective treatment has been delivered. Artificial ventilation requires sedation, and the present propofol formulations can be used for this purpose. Simultaneously, the present propofol formulations can improve survival potential by a mechanism that is independent of the artificial ventilation.

Combination with other therapeutic agents

As a further feature of the present invention there are provided pharmaceutical compositions containing free radical scavenging sedatives (such as propofol) suitable for use in the present invention for parenteral administration which comprises, for example, an oil-in-water emulsion, containing a therapeutic or pharmaceutical agent, in which the agent, either alone or dissolved in a water-immiscible solvent, is emulsified with water and a free radical scavenging sedatives (such as propofol), and stabilised by means of a surfactant and which further comprises a metal ion chelating agent.

Suitable therapeutic or pharmaceutical agents are those capable of being administered parenterally in an oil-in-water emulsion. Typically such agents (which may be administered separately, sequentially or simultaneously with the propofol composition) are lipophilic compounds and may for example be antifungal agents, anaesthetics, antibacterial agents, anti-cancer agents, anti-emetics, antioxidants, agents acting on the central nervous system such as diazepam, steroids, barbiturates and vitamin preparations. The agents most useful are those which may have additional benefit in the treatment or prevention of multiple organ dsyfunction and death and its causes, for example, antibacterial agents, NSAIDs, Vitamin E, fluid therapy and vasoactive amines. Supportive treatment of organ insufficiency may include artificial ventilation and dialysis.

Thus, there is provided the use of a pharmaceutical compositions containing a free radical scavenging sedative (such as propofol) for parenteral administration which comprises, for example, an oil-in-water emulsion, containing a therapeutic or pharmaceutical agent, in which the agent, either alone or dissolved in a water-immiscible solvent, is emulsified with water and a free radical scavenging sedative (such as propofol), and stabilised by means of a surfactant and which further comprises an amount of a metal ion chelating agent, for the manufacture of a medicament for improving survival in critically ill patients. Also provided is a method of improving survival in critically ill patients comprising the use of such compositions. In particular this feature of the present invention relates to such oil-in-water

emulsions which typically are administered, to patients in need thereof, over periods of a day or more.

Comments herein relating to typical and preferred propofol compositions for use in the present invention and the preparation thereof apply mutatis mutandis to oil-in-water emulsions containing an additional therapeutic or pharmaceutical agent.

EXPERIMENTAL & RESULTS

The data from four clinical trials indicating an improvement in survival in certain critically ill patients is summarised in Table 1.

The programme included four studies in adult ICU sedation. Three of these studies compared 1% original formulation 'Diprivan' versus modified formulation 'Diprivan'. These were Study 53: in surgical ICU patients (SICU), Study 54: in medical ICU patients (MICU) and Study 60: in patients with renal failure. The fourth study, Study 69 was a comparison of modified formulation 'Diprivan' against standard sedative agents (SSAs, without EDTA) in medical, trauma and surgical ICU patients.

Table 1 ICU Survival Data for original and modified formulation 'Diprivan'

			To 7-day follow-up				To 28-day follow-up			
Trial	Treatment Formulation	No. pats.	No. deaths	% deaths	% survival	p-value	No. deaths	% deaths	% survival	p-value
53	modified	59	0	0	100	0.006	1	2	98	0.004
	original	63	8	13	87		11	17	83	
54	modified	42	9	21	79	0.459	19	45	55	1.000
	original	43	13	30	70		19	44	56	
60	modified	18	4	22	78	1.000	5	28	72	0.728
	original	19	4	21	79		7	37	63	
69	modified	106	18	17	83	0.303	33	31	69	0.768
	SSA	104	24	23	77		35	34	66	

The follow-up was timed from the end of ICU sedation.

Analysis of mortality from these studies were not primary measures.

Study 53, in surgical patients, shows in particular that there was a statistically significantly lower ($p = 0.006$) mortality at 7-day follow-up in those patients receiving modified formulation 'Diprivan' (0/59 patients) compared to those receiving original formulation 'Diprivan' (8/63 patients). At 28-days there was also a significantly lower mortality rate in the modified formulation group.

In other studies, the mortality benefit although perhaps not statistically significant, may be less apparent for a number of reasons. For example, such reasons may include low patient numbers, patients considered to be severely ill (such as severe renal failure patients) and so unlikely to benefit from the invention (which is of particular benefit for critically ill patients), or the duration of treatment is too short for a benefit to be observed. Futhermore, in Study 53 patients were administered with the propofol formulations early in the course of each patient's illness (i.e. immediately post-operatively), whereas administration was later in the course of illness in the other studies. Thus, greater outcome benefit may be provided when the modified formulation 'Diprivan'is administered early in the course of critical illness (i.e. when the systemic inflammatory response is not fully activated).

Propofol and EDTA administration in these studies is summarised below (ZD#1 = modified formulation; DIP = original formulation).

Table 2A : Propofol Infusion Rates (mcg/kg/min)

Trial No.	Treatment group	N	Mean	Range
53	ZD#1	59	31.64	2.37 -79.31
	DIP	62	32.18	4.5 - 72.85
54	ZD#1	42	40.27	2.84 - 105.26
	DIP	40	34.51	6.43 - 123.67
60	ZD#1	18	7.89	1.99 - 17.09
	DIP	19	12.62	0.86 - 45.91
69	ZD#1	106	36.0	3.3 - 154.3
Overall	ZD#1			0.86 - 154.3
	DIP			1.99 - 123.67

Table 2B : EDTA Infusion Rates (ng/kg/min)

Trial No.	Treatment group	N	Mean	Range
53	ZD#1	59	158.18	11.86 - 396.54
54	ZD#1	42	201.33	14.18 - 526.31
60	ZD#1	18	39.47	9.93 - 85.44
69	ZD#1	106	179.8	16.7 - 771.3
Overall	ZD#1			9.93 -771.3

In Study 53 the mean total dose of EDTA received was 39.1 ± 82.91 mg.

Table 2C : Duration of sedation (hrs)

Trial No.	Treatment group	N	Mean	Range
53	ZD#1	59	41.51	2.0 - 308.5
	DIP	63	43.74	0.92 - 503.25
54	ZD#1	42	111.31	7.83 - 362.42
	DIP	40	95.57	12.25 - 483.77
60	ZD#1	18	74.07	4.0 - 265.42
	DIP	19	69.58	23.0 - 122.33
69	ZD#1	106	149.1	6.7 - 645.0
Overall	ZD#1			2.0 - 645.0
	DIP			0.92 - 503.25

Analysis of survival for Studies 53, 54 & 60

Patients in each of the three studies were randomized to receive 1% propofol in aqueous emulsion, i.e. original formulation 'Diprivan' (control group) or propofol-EDTA, i.e. modified formulation 'Diprivan' (treatment group). All trials were conducted in compliance with regulations governing informed consent, and institutional review board approval was obtained at all participating institutions. All patients provided written informed consent prior to enrollment in the studies.

For all three studies, patients who had a history of hypersensitivity to the trial drug or any of its constituents or who had participated in another investigational drug trial within 30 days of study entry were excluded from participation.

Study 53

SICU patients who were 17 years of age or older, hemodynamically stable, and expected to require intubation and mechanical ventilation for at least 2 hours were eligible for inclusion in the trial. Patients were ineligible for the study if they were unable to respond to stimuli because of prolonged paralysis due to trauma or neuromuscular blockade.

Study 54

Eligible patients were men and women 13 years of age or older who were admitted to the ICU with pulmonary dysfunction or adult respiratory distress syndrome (ARDS) as one of their primary diagnoses or complications, hemodynamically stable, expected to require at least 48 hours of sedation and mechanical ventilation.

Study 60

Eligible patients consisted of SICU or MICU patients with documented impaired renal function (estimated creatinine clearance ≤40 mL/min) who were 17 years of age or older, hemodynamically stable, and expected to require intubation and mechanical ventilation for ≥24 hours, and who had achieved adequate levels of postoperative analgesia (SICU patients only). Exclusion criteria included head trauma and an inability to respond to stimuli because of paralysis.

Patients were randomised to receive either propofol or propofol-EDTA. Sedation was initiated by continuous infusion at an initial rate of 5 μg/kg/min. and then was adjusted until the patient achieved the required level of sedation. The sedative dose could be adjusted to change the level of sedation for short periods of time and in addition the level of sedation

could be changed by the investigator if a different level of sedation was considered more appropriate for the patient.

If possible, trial drug was administered to patients continuously until extubation was anticipated. During the weaning period, either propofol or propofol-EDTA could be administered to provide a light level of sedation. If the patient met adequate criteria for extubation at the end of weaning from mechanical ventilation, the trial drug was discontinued and the patient extubated.

For all studies, standard non-sedating medications that were considered necessary and were not expected to interfere with the trial drug or affect trial measurements were given at the discretion of the investigator. Enteral nutrition was the preferred form of nutritional support, but parenteral nutrition was also permitted.

For SICU and MICU patients, only morphine sulfate and fentanyl were permitted for analgesia. For renal failure patients, adequate analgesia was provided postoperatively before the start of propofol or propofol-EDTA infusion. During sedation, patients received an epidural or intravenous infusion of fentanyl for analgesia. In patients who were receiving lipid infusion for nutritional supplementation, the quantity of concurrently administered lipids was reduced to compensate for the amount of lipid infused as part of the propofol and propofol-EDTA formulations.

Demographic variables and treatment descriptors were compared to assess comparability of the propofol and propofol-EDTA groups. Chi-square analysis was used for the categorical variable (sex), and Wilcoxon test (using normal approximations and continuity corrections of 0.5) was used for continuous variables (such as age, body weight, APACHE II score, total propofol dose, mean propofol infusion rate, and duration of infusion). Gender, age, body weight, and severity of illness as indicated by APACHE II score did not differ significantly between the propofol and propofol-EDTA groups.

Median total propofol dose, median infusion duration and mean infusion rate were not significantly different between groups. There were also no significant differences between the propofol and propofol-EDTA groups in any of the laboratory values measured. Serum ionized calcium and magnesium, intact PTH, 1,25-dihydroxyvitamin D, sodium, potassium, and phosphate levels, as well as renal function (as assessed by BUN and serum creatinine levels), were similar in both groups. Blood pressure and heart rate were similar between the propofol and propofol-EDTA groups.

Survival was summarized by counting the number of patients alive and calculating descriptive statistics for the survival times of patients who died. Product-limit (Kaplan-Meier) estimates of the survival function were calculated for both the propofol and propofol-EDTA groups within each study population (SICU, MICU, and renal failure patients). Survival curves were also compared between the two groups within each study population using the log-rank test and Wilcoxon's test.

Figure 1 shows survival curves by treatment group (propofol or propofol-EDTA), study population (SICU, MICU, or renal failure), and baseline APACHE II score (<15, 15–24, or >24).

Figure 2 shows predictions of survival based on a model incorporating the influence of study population, baseline APACHE II score, and treatment effect. For patients with an APACHE II score of 11, the model predicts an improvement in survival for SICU patients receiving propofol-EDTA (Figure 2A). For patients with an APACHE II score of 21, overall survival is expected to be worse than in patients with an APACHE II score of 11, but the use of modified formulation 'Diprivan' is predicted to improve survival in both SICU and renal failure patients (Figure 2B). For patients with an APACHE II score of 30, the model predicts that modified formulation 'Diprivan' will considerably improve survival in SICU patients (Figure 2C).

Cox proportional hazards regression analysis was used to model the influence of predictors of survival. The model predicts the survival time, T, based on a survival function, $S(t) = Pr(T > t)$, where the hazard rate, $h(t) >> Pr(t < T, t + dt \mid T > t)/dt$. The actual hazard model was $\log h(t) = \log h_0(t) + bx$, where the baseline hazard was unspecified.

The null model was a model stratified by patient population (i.e. a model that allowed a different baseline hazard function for patients in the SICU, MICU, and renal failure groups, without the restriction that these three hazards be proportional). To the null model was added APACHE II score, with a different slope and intercept for each of the three studies, and the treatment variable (propofol only versus propofol-EDTA). The treatment effect was allowed to differ among the three studies. Other factors significantly affecting survival were determined by stepwise addition of age, sex, height, body weight, serum albumin level, total propofol dose, mean propofol infusion rate, median duration of infusion, SAPS II, patient type

(medical versus surgical), and medical history (malignancy versus other) to the model. Statistical computations were carried out using SAS for Windows version 6.12.

Figure 3 summarizes the results of the Cox proportional hazards model. The linear predictor on the y-axis is the extent to which mortality is expected to increase with each predictor. The x-axis reflects the widespread influence of APACHE II score on survival. In the SICU study population, the addition of EDTA produced an effect equivalent to decreasing the APACHE II score from 38 to 10. In renal failure patients, the effect produced by use of modified formulation 'Diprivan' depended on APACHE II score. In patients with an APACHE II score <25, survival is predicted to improve with modified formulation 'Diprivan'; in patients with an APACHE II score >30, survival is expected to worsen.

The results of this analysis indicate that modified formulation 'Diprivan' significantly improves survival in critically ill surgical patients; its effect on survival in renal failure patients is variable, with patients with APACHE II scores <24 having improved survival, but patients with APACHE II scores >24 having lower rates of survival.

In this study we found no evidence of EDTA-induced renal toxicity as assessed by BUN and creatinine levels.

The major finding of this study is the improved survival rate in SICU patients receiving modified formulation 'Diprivan', compared with original formulation 'Diprivan'.

The mortality rate for the SICU propofol group was close to that predicted, whereas the rate for the SICU propofol-EDTA (modified formulation 'Diprivan') group was lower than expected, thereby indicating a beneficial therapeutic effect.

It is unclear why MICU and severe renal failure patients failed to realize the same benefit from modified formulation 'Diprivan' seen in SICU patients. In SICU patients, critical illness was of more acute onset, and treatment with modified formulation 'Diprivan' began sooner after the critical insult than in MICU patients. It is possible that organ injury was more advanced in MICU and renal failure patients than in SICU patients, causing modified formulation 'Diprivan' to have a decreased therapeutic benefit. MICU and renal failure patients also appeared to have more serious and longer duration of disease prior to admission to the ICU. It is also likely that malnutrition was greater in these patients. Furthermore, it is possible that MICU patients had underlying deficiencies of trace minerals

than SICU patients, and renal patients with high APACHE II scores probably had more advanced renal disease.

The results of this study suggest that modified formulation 'Diprivan' may have a beneficial therapeutic effect in select groups of critically ill patients, with the greatest effect on survival occurring in SICU patients. The benefits of modified formulation 'Diprivan' in SICU patients were sufficiently large to suggest that modified formulation 'Diprivan' may represent a potential new therapy for the treatment of critically ill patients with systemic inflammatory response syndrome.

Summary of Figures :

Figure 1 : Survival curves by treatment group (A), study population (B) and APACHE II score (C) : ZD = modified formulation; DIPRIVAN = original formulation

Figure 2 : Prediction of survival based on a model incorporating the influence of study population and treatment effect for APACHE II scores of 11 (A), 21 (B), and 30 (C)
SICU–no EDTA = SICU patients who received propofol;
SICU–EDTA = SICU patients who received propofol-EDTA;
renal failure–no EDTA = renal failure patients who received propofol;
renal failure–EDTA = renal failure patients who received propofol-EDTA;
MICU = MICU patients who received either propofol or propofol-EDTA (all MICU patients grouped together).

Figure 3 : Results of Cox proportional hazards model
The linear predictor on the y-axis is the extent to which mortality is expected to increase with each predictor. The widespread influence of APACHE II score on survival in all groups is evident.

SICU–no EDTA = SICU patients who received propofol;
SICU–EDTA = SICU patients who received propofol-EDTA;
renal failure–no EDTA = renal failure patients who received propofol;
renal failure–EDTA = renal failure patients who received propofol-EDTA;
MICU = MICU patients who received either propofol or propofol-EDTA (all MICU patients grouped together).

Clinical Trial

The benefits disclosed herein can be demonstrated in a prospective study with mortality as the primary endpoint, comparing modified formulation 'Diprivan' against e.g. original formulation 'Diprivan'.

The trial treatment is intravenous infusion of propofol commencing at 5μg/kg/min. and titrated to achieve the depth of sedation considered appropriate by the investigator. Randomisation of patients is post-operative and the study uses 1% strength modified formulation 'Diprivan'. Note that the benefit is also believed to attach to 2% strength (in which the amount of disodium edetate is half that in an equivalent propofol dose of the 1% strength).

The trial is designed with 250 patients in each arm (to give an 80% probability and $p < 0.05$ significance level), for 28-day mortality in the original formulation 'Diprivan' arm of 17.5% and in the modified formulation 'Diprivan' arm of 8.6% (i.e. an absolute reduction of 8.9% or a relative reduction of 51%).

Trial summary :

A multicentre randomised comparison of mortality in adult surgical ICU patients (minimum age 18 years and requiring sedation for endotracheal intubation for at least 24 hours) sedated with original formulation 'Diprivan' versus modified formulation 'Diprivan', to compare 28-day mortality in adult surgical ICU patients sedated with original formulation 'Diprivan' versus modified formulation 'Diprivan'. Patients with head injury or those who have had an established regimen of sedation with agents other than Diprivan in the period immediately preceding consideration for the study will be excluded.

The primary endpoint is severity-adjusted 28-day mortality, i.e. death during sedation and within 28 days from start of (post-operative) sedation irrespective of duration of sedation (but with a minimum duration of treatment of 24 hours). The primary endpoint thus includes patients sedated for 1 day and then dying on day 27 since commencement of sedation, as well as patients sedated for 10 days and dying on day 27 since commencement of sedation.

Secondary endpoints include sequential organ failure assessment 7- & 28-days following start of sedation and time on ventilation.

Data to be recorded include patient demographics, past history, medications (with a restriction on concomitant medication having no EDTA), reason for surgery, type of anaesthesia (with a restriction on the surgical anaesthetic having no EDTA), SAPS II and

SOFA at baseline, 7- and 28-days, duration of sedation (and ventilation) and total dose of propofol and adverse events.

Claims

What is claimed is :-

1. A pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier, for use as a medicament for improving survival in a critically ill patient.

2. A sterile pharmaceutical composition for parenteral administration, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent, for use as a medicament for improving survival in a critically ill patient.

3. A sterile pharmaceutical composition, according to claim 1 or 2, in which the metal ion chelating agent is edetate, for use as a medicament for improving survival in a critically ill patient.

4. The use of a sterile pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent for the manufacture of a medicament for improving survival in a critically ill patient.

5. The use, according to claim 4, of a sterile pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier, for the manufacture of a medicament for improving survival in a critically ill patient.

6. The use, according to claim 4 or 5, which composition comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent, for the manufacture of a medicament for improving survival in a critically ill patient.

7. The use, according to any one of claims 4 to 6, in which the metal ion chelating agent is edetate.

8. The use, according to any one of claims 4 to 7, in which the sterile pharmaceutical composition is in the form of an oil-in-water emulsion which comprises:

(a) 1% by weight of propofol,
(b) 10% by weight of soy bean oil,
(c) 1.2% by weight of egg phosphatide,
(d) 2.25% by weight of glycerol,
(e) sodium hydroxide,
(f) water,
(g) 0.005% by weight of disodium edetate.

9. The use, according to any one of claims 4 to 7, in which the sterile pharmaceutical composition is in the form of an oil-in-water emulsion which comprises:

(a) 2% by weight of propofol,
(b) 10% by weight of soy bean oil,
(c) 1.2% by weight of egg phosphatide,
(d) 2.25% by weight of glycerol,
(e) sodium hydroxide,
(f) water,
(g) 0.005% by weight of disodium edetate.

10. The use, according to any one of claims 4 to 9, in which the critically ill patient is a surgical patient.

11. A method for improving survival in a critically ill patient which comprises administration to such patient of an effective amount of a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent.

12. A method, according to claim 11, for improving survival in a critically ill patient which comprises administration of a pharmaceutical composition comprising a free-radical scavenging sedative agent and a metal ion chelating agent, in association with a pharmaceutically-acceptable diluent or carrier.

13. A method, according to claim 11 or 12, which comprises administration of a pharmaceutical composition comprising an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilised by means of a surfactant, and which further comprises a metal ion chelating agent.

14. A method, according to any one of claims 11 to 13, in which the metal ion chelating agent is edetate.

15. A method, according to any one of claims 11 to 14, in which the pharmaceutical composition is as defined in claim 8 or 9.

16. A method, according to any one of claims 11 to 15, in which the critically ill patient is a surgical patient.

Figure 1

Survival curves by treatment group (A), study population (B) and APACHE II score (C)

ZD = modified formulation; DIPRIVAN = original formulation

Fig.1A

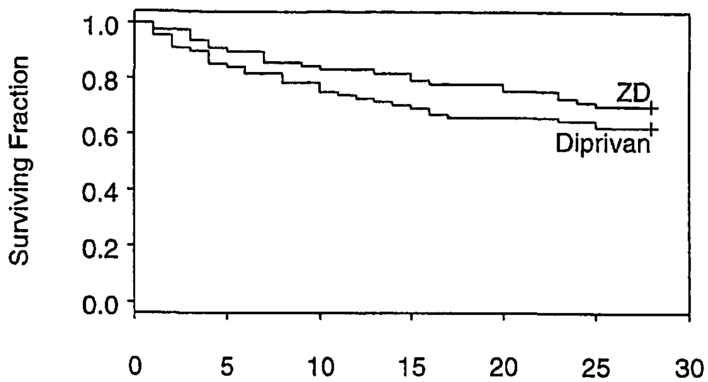

Fig.1B

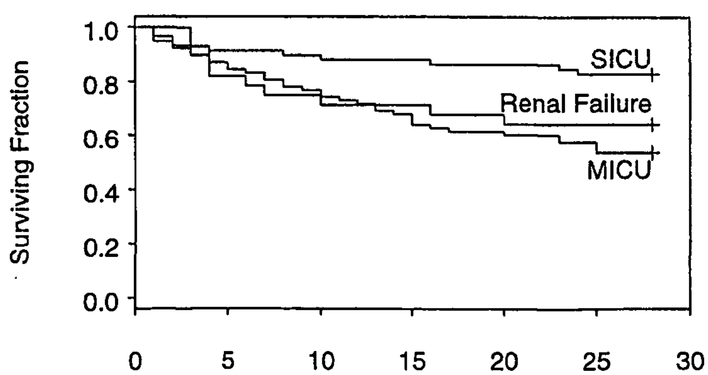

Figure 1 (continued)

Survival curves by APACHE II score (C)

Fig.1C

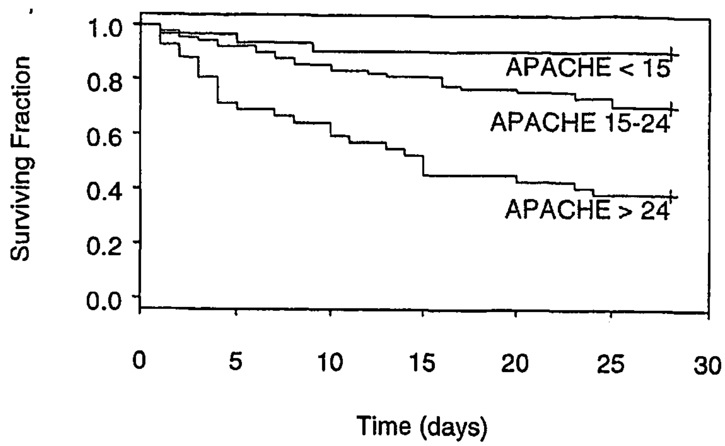

Figure 2

Prediction of survival based on a model incorporating the influence of study population and treatment effect for APACHE II scores of 11 (A), 21 (B)

SICU–no EDTA = Surgical ICU patients who received propofol;

SICU–EDTA = SICU patients who received propofol-EDTA;

renal failure–no EDTA = renal failure patients who received propofol;

renal failure–EDTA = renal failure patients who received propofol-EDTA;

MICU = Medical ICU patients who received either propofol or propofol-EDTA (all MICU patients grouped together).

Fig.2A

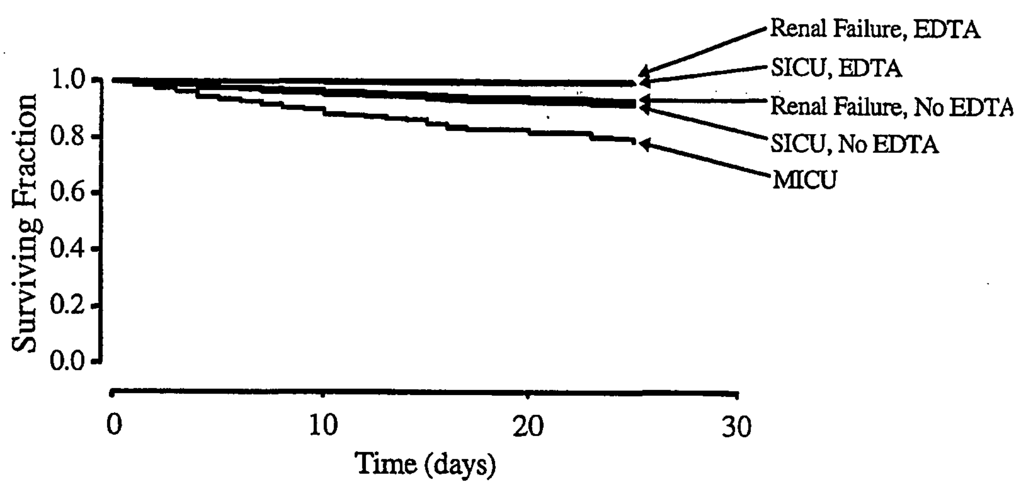

Fig.2B

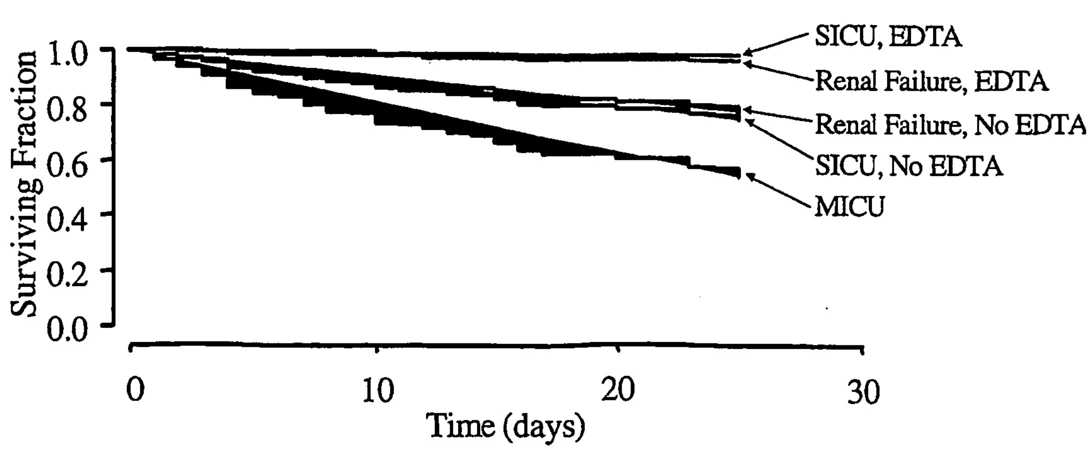

Figure 2 (continued)

Prediction of survival based on a model incorporating the influence of study population and treatment effect for APACHE II score of 30 (C)

SICU–no EDTA = Surgical ICU patients who received propofol;

SICU–EDTA = SICU patients who received propofol-EDTA;

renal failure–no EDTA = renal failure patients who received propofol;

renal failure–EDTA = renal failure patients who received propofol-EDTA;

MICU = Medical ICU patients who received either propofol or propofol-EDTA (all MICU patients grouped together).

Fig.2C

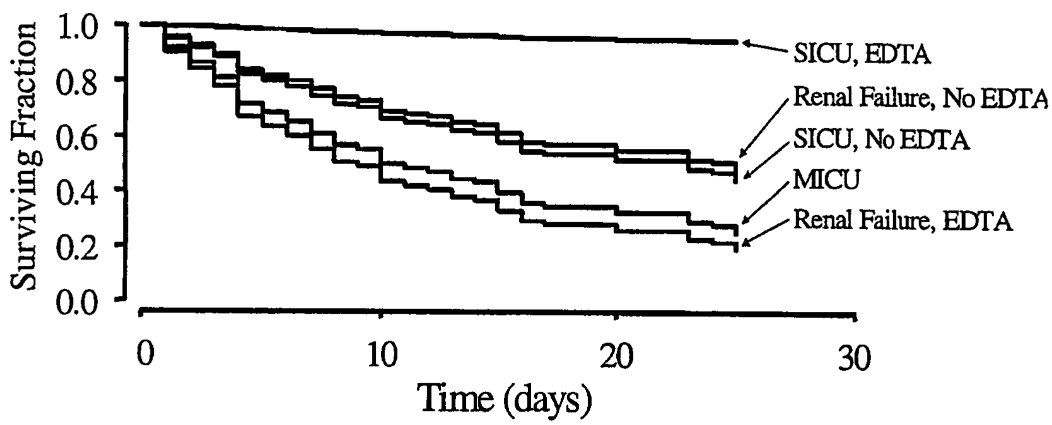

Figure 3

Results of Cox proportional hazards model

The linear predictor on the y-axis is the extent to which mortality is expected to increase with each predictor.

SICU–no EDTA = Surgical ICU patients who received propofol;
SICU–EDTA = SICU patients who received propofol-EDTA;
renal failure–no EDTA = renal failure patients who received propofol;
renal failure–EDTA = renal failure patients who received propofol-EDTA;
MICU = Medical ICU patients who received either propofol or propofol-EDTA (all MICU patients grouped together).